REMARKS/ARGUMENTS

By the present amendment, claims 13, 17, 22 and 50-53 have been amended as described below. Claims 12, 13, 17, 22, 50-53 are pending in the present application. The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. The Applicants reserve the right to file any of the canceled subject matter in a divisional patent application. The Applicants submit that no new subject matter has been added by way of the present amendment and entry of the claim amendments is respectfully requested.

The Office Action dated April 28, 2008 has been carefully considered. It is believed that the claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Claim Objections

The Examiner has objected to claims 13, 17, 50-53 for reciting "A method" instead of "The method". Claims 13, 17, 50-53 have been amended as suggested by the Examiner. In light of the above, the Applicant respectfully requests that the objections to these claims be withdrawn.

35 USC § 112

The Examiner has objected to claims 22, 52 and 53 as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Specifically, the Examiner alleges, as recited it is unclear what reference point the number of cells increased at least about 10 to 15 fold is compared to. Accordingly, claim 22 has been amended to state "when the number of cells is increased at least about 10 to 15 fold compared to the stem cells or progenitor cells cultured in step a)". Claims 52 and 53 depend on independent claim 22 and thereby incorporate the above amendment. In light of the above the Applicant respectfully requests that the objection under 35 USC § 112 be withdrawn.

35 USC § 103

The Examiner has rejected claims 12-13, 17, 50, 51 and 22, 55 and 53 as being unpatentable over Jaleco et al. (2001, J. Exp. Med. 194:991-1001, IDS); Nakano et al. (1994, Science 265:5157 IDS); Pui et al. (Immunity, 1999, 11(3):299-308), and Tatsumi et al. (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS). We respectfully disagree with the Examiner for the reasons that follow.

As a first matter, the Examiner alleges on page 4 that one of ordinary skill "who would modify the method of Jaleco et al. to substitute S-17 stromal cells that express DL-1 with another OP-9 would implicitly observe higher numbers of immature T lineage cells". Thus, the Examiner states the subsequent analysis is limited to the extent claims read on a method of culturing human progenitor/stem cells with OP-9 stromal cells that express Delta-1 DL-1 to produce mature and immature/mature T cell lineage cells.

The Examiner states that he agrees with the Applicant's assertion that Jaleco et al. teaches that culturing human progenitor cells with mouse S-17 stromal cells that express Delta-1 (S-17-DL1) produces low levels of CD3+CD4+CD8+ T-lineage cells. The Examiner then states that the low levels of these double positive T cells supports the argument that co culturing progenitor cells with stromal cells that express DL-1 to study T-lineage cells was known in the prior art. The Applicant respectfully disagrees. However, in order to expedite prosecution, claim 22 has been amended to remove reference to CD3+CD4+CD8+ cells. Therefore, the amended claims do not recite T cell types disclosed in Jaleco et al.

The Examiner maintains the position that substitution of S-17 stromal cells taught by Jaleco et al. with OP-9 DL-1 stromal cells would be prima facie obvious to one of ordinary skill in the art. The Examiner adds that with respect to OP-9, it was generally known that OP-9 stromal cells provide a practical model system for the induction of lymphopoiesis from several sources of progenitors. For example, the Examiner states that Nakano et al. provide guidance with respect to OP-9 cells that could support the

hematolymphopoiesis from embryonic stem cells, while Pui et al. provided evidence that indicated a crucial role for Notch signaling in the T versus B-cell fate decision. The Examiner concludes that given that it was known to one of ordinary skill the important role for Notch signaling at various stages of T-cell development, it is reasonable to state that one of ordinary skill in the art would substitute S-17 stromal cells with OP-9 cells that express DL-1 in determining the fate or generation of T-cells. The Applicant respectfully disagrees. In each prior art case referred to above, the Examiner refers to lymphopoiesis and not T cell lineage development or refers to Notch as opposed to the specific Notch ligands claimed. Nakano et al. provided guidance regarding B-cell development, Pui et al. showed that B-cell development is abolished in mice that are reconstituted with bone marrow progenitors expression of institute of active form of Notch. Neither of these references however, provide any indication or any teaching that the Notch ligands DL-1 or DL-4 are sufficient for generating and/or expanding T-cells. Pui et al. does not provide any guidance in the use of Notch ligands at all. Two distinct families of Notch ligands are known, each of which comprise several family members. The Examiner adds "Jaleco et al. provided guidance on a method of using an *in vitro* system comprising stromal cells that also promoted selective differentiation of CB CD34+ cells into the B-cell lineage, but when these cells were co cultured with S-17 cells that were modified with Delta-1 ligand to support T-cell lymphopoiesis of human hematopoietic progenitor cells (HPCs) without supporting B-cell lymphopoiesis (Abstract, pg 995, Table 1)" (emphasis ours). Nowhere in the abstract, on page 995 or in Table 1 does Jaleco et al. indicate that S-17 cells were modified with Delta-1 to support T-cell lymphopoiesis. Jaleco et al. state that the plurality of Notch receptors and Notch ligands may translate into functional diversity of Notch actions in vivo (pg. 992, bottom left column). The Examiner is applying hindsight analysis which is impermissible.

The Examiner further alleges that given that Pui et al. teaches constitutive expression of activated Notch 1 results in the emergence of a population of thymic independent T-cells in the bone marrow concurrent with an early and persistent block in B-cell maturation, it would be apparent to one of ordinary skill in the art to substitute one

stromal cell that expresses Notch ligand DL-1 with another stromal cell such as OP-9 that expresses Notch ligand to study the role of T-cell lymphopoiesis of human hematopoietic progenitor cells with reasonable expectation of achieving predictable results. The Applicant respectfully disagrees. As mentioned, Pui et al. does not discuss any ligand. Nowhere in Pui et al. and/or Jaleco et al. is it suggested alone or in combination that DL-1 would be sufficient.

The Examiner also asserts that given the knowledge that a constitutively active form of Notch abolishes B-cell development and instead allows CD4+CD8+ DP T-cells to develop in bone marrow and that Notch signals have been shown to promote the development of $\alpha\beta$T-cell lineage over the $\gamma\delta$T-cell lineage for T-cell fate decision "it is reasonable to assert that it is not only stromal cell but stromal cell that expresses Notch ligand that has a crucial roll in T-cell lineage commitment and differentiation". As mentioned, there are a number of Notch ligands. The Examiner is using impermissible hindsight selection of which ligand would be necessary and whether one ligand and/or DL-1 and/or DL-4 would be sufficient in any stromal cell line to promote T-cell development. The Examiner further adds that it would have been obvious for one of ordinary skill in the art to substitute one stromal cell SL-17 that expresses DL-1 with another functional equivalent stromal cell such as OP-9. However, if OP-9 was indeed functionally equivalent to SL-17 then SL-17 would also produce the T-cell lineage cells described in the instant claims. This is clearly not the case. Accordingly identifying a stromal cell such as OP-9 that can produce cells of the T-cell lineage as described in the instant claims involves inventive skill.

It is clearly not predictable based on the combined teachings of the art that any stromal cell expressing DL-1 or DL-4 would result in increased numbers of cells of the T-cell lineage (as per claim 22) and/or mature cells of the T-cell lineage (as per claim 12). In this regard, we enclose a copy of a recent publication in the Journal of Immunology (Mohtashami and Zuniga-Pflucker, The Journal of Immunology, 2006, 176:730-734) which demonstrates that expression of DL-1 or DL-4 in NIH3T3 cells is insufficient to support T-cell development (see page 733, left column, top paragraph). In addition, the

authors show NIH3T3 cells expressing DL-1 or DL-4 did not support the generation of the B-lineage cells from HPCs in contrast to NIH3T3 cells expressing GFP which do (see Figure 5). Therefore, this paper shows that cells that normally support B-cell development (such as NIH3T3 cells) do not necessarily support T cell development when transfected with DL-1 or DL-4. As a result, the teachings of Nakano which state that OP-9 cells support B-cell development would provide no expectation of success that the same cells could be used in the present invention. In addition, the attached paper provides further evidence that not all cells expressing DL-1 or DL-4 are useful in generating T cells. This is consistent with the findings of Jaleco et al. Further, as Jaleco et al. does not teach or suggest the generating of the T cells as claimed in the present claims, one of ordinary skill in the art would not predict that S-17 cells could be replaced with OP-9 cells to generate the claimed T cells with a reasonable expectation of success.

With respect, the Examiner has failed to establish a prima facie case of obviousness in the present case. The Supreme Court recently addressed the proper standard for obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). There, the Court held that the proper question for evaluating obviousness is "whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR*, 127 S.Ct. at 1741. The Federal Circuit considered the "reason" requirement in *Takeda Chem. Industs., Ltd. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (2007), reversing an obviousness finding when the claims recited a specific chemical compound and "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." The court emphasized that obviousness requires that the prior art give a reason or motivation to make the specific composition claimed. *Takeda*, 492 F.3d at 1356.

Thus, for a proper combination of references, there must be some indicative teaching or suggestion in the prior art. MPEP § 2142. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP § 2143.01.

The references cited by the Examiner together fail to suggest using OP-9 cells expressing DL-1 or DL-4 to produce the claimed T-cells. The cited art evidence no motivation to have combined the teachings in question, as asserted, in order to arrive at the claimed invention. **In short, no combination of cited references could have provided a reasonable (i.e., a principled) expectation that OP-9 cells expressing DL-1 or DL-4 can be used to prepare the claimed T cells.** With respect, the Examiner has failed to prove otherwise.

In light of the above, the Applicant respectfully requests that the objection under 35 USC § 103 be withdrawn.

The Commissioner is hereby authorized to charge any deficiency in fees (including any claim fees) or credit any overpayment to our Deposit Account No. 02-2095.

In view of the foregoing, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, she is kindly requested to contact Micheline Gravelle by telephone at 416-957-1682 at his/her convenience.

Respectfully submitted,

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